REMARKS

Formal Matters

Claims 17-22 and 24-35 and 37-44 are pending after entry of the amendments set forth herein.

Claims 17-22 and 24-44 were examined. Claims 17-22 and 24-44 were rejected.

Claims 30 and 37 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. The subject matter of claim 36 has been incorporated into claim 30, and, as such, no new matter is added by these amendments.

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow the claims.

Interview summary

Telephonic interviews between the Applicant's representative James Keddie and Supervisory Exr. Gary Benzion were held on May 16, 20 and 27, 2003.

The rejection of claims 17-20, 24-26, 28-32 and 36-41 under 35 U.S.C. §103(a) as obvious over Martin, in view of Cao and the Stratagene Catalog, as set forth below, was discussed. In particular, the question of whether a skilled person would be motivated to combine the cited references was addressed. Exr. Benzion agreed that the motivation set forth in the Office Action (i.e., Cao's statement that "The identification of the gene for the second E. coli poly(A) polymerase ***opens the way for the detailed investigation*** of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes", emphasis added) was insufficient to establish a *prima facie* case of obviousness since it is merely an "invitation to explore". Exr. Benzion indicated that the rejection would be withdrawn.

Applicants note that this rejection has been maintained, and respectfully request that withdrawal of this rejection is re-considered in view of the above comments. The Applicants previously made arguments are re-iterated below, and Exr. Chakrabarti is respectfully requested to discuss the rejection with Exr. Benzion before responding.

Exr. Benzion also indicated that a discussion of known prokaryotic poly(A) polymerases, particularly with regard to their structure/function relationship, may be

sufficient to overcome a new rejection based on an asserted lack or written description, as set forth in this Office Action.

Claim Rejections- 35 U.S.C. §112, first paragraph (written description)

Claims 17-20 and 24-44 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time of the application was filed had possession of the claimed invention. The rejection is based on the assertion that there is no disclosure of the detailed chemical structure of the encompassed enzymatic proteins, or for any domains required for poly(A) polymerase activity. The Applicants respectfully traverse this rejection.

The Written Description Guidelines (Federal Register vol. 66, 4, 2001), to which Examiners must adhere when making a determination of whether a specification adequately describes a claimed invention, states "Information which is well known in the art need not be described in detail in the specification" and, "The description need only describe in detail that which is new or not conventional"[1] In other words, there is no requirement for a detailed description of something which is known.

The Applicants respectfully submit that prokaryotic poly(A) polymerases were well known at the time of filing, and, as such, they have met the requirements set forth in the Written Description Guidelines.

Support for this assertion is as follows: the amino acid sequences of at least 17 prokaryotic structurally related poly(A) polymerases were known at the time of filing (shown in Table 1 of Aravind et al. Nucl. Acids Res. 1999, 27:1609-1618; Exhibit A). Further, prokaryotic poly(A) polymerases have a well known and well recognized domain called a "poly(A) polymerase domain" which is found in all prokaryotic poly(A) polymerases. This domain is exemplified in Exhibit B, which shows an entry from NCBI's "Conserved Domain Database". In view of the foregoing discussion, the Applicants respectfully submit that prokaryotic poly(A) polymerases were well known at the time of filing of the instant patent application, and, as such, do not need to be described in any detail. As such, the Applicants respectfully submit that they have met this requirements for written description set forth in the Written Description Guidelines.

Further, because prokaryotic poly(A) polymerases all have a poly(A) polymerase domains that are similar to each other, they can be classified as a poly(A) polymerase on the basis of their sequence (see e.g. Table 1 of Exhibit A, and Exhibit B). This is well known in the art. As such, by reciting a "poly(A) polymerase", the Applicants have set forth distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the invention.

With respect to the structure-function relationship of prokaryotic poly(A) polymerase proteins, Exhibit A, from NCBI's Conserved Domain Database, is an alignment of 9 exemplary prokaryotic poly(A) polymerase proteins, including those of the following bacteria: *Synechocystis, Aquifex, Thermus thermophilus, Synechocystis, Treponema pallidum, Chlamydia trachomatis, and Borrelia burgdorferi.* This alignment of indicates a well-defined conserved domain for bacterial poly(A) polymerases, and indicates that the structure-function relationship for prokaryotic poly(A) polymerase proteins is known. Furthermore, at the time of filing, the particular amino acid that form the catalytic domain and RNA binding sites of prokaryotic polyA polymerases were defined (see, e.g., Fig. 1 of Raynal, Mol. Microbiol. 1999 32:765-75, Exhibit C).

As such, a skilled person would recognize that the prokaryotic polyA polymerases recited in the claims are very well known and are structurally related to each other. Accordingly, a skilled person would recognize that the inventors, by reciting a genus of poly(A) polymerases for which several members are known, had possession of the claimed invention in its full scope.

The Office Action further asserts that the specification does not meet the written description requirement of 35 U.S.C. §112 because all non-radioactive labels such as biotin and avidin are not specifically mentioned in the application. The Applicants respectfully submit that even in an unpredictable art, the Applicants "are *not* required to disclose *every* species encompassed by their claims . . . ."[1] Otherwise, to claim a genus, every species within a genus would have to be explicitly described. This is **not** the law. In other words, the written description requirement does not require a specific description of every species encompassed by a claim.

[1] *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218, (C.C.P.A. 1976).

As such, according to the law of written description, a recitation of all non-radioactive labels that could be encompassed by the claims is not required for the claims to meet the legal standards for written description. As such, the fact that the specification does not mention biotin or avidin has no bearing on the patentability of the instant claims, especially in view of the extensive description of suitable labels found on pages 6-14.

The Applicants respectfully submit that this description of suitable non-radioactive labels is sufficiently extensive to meet requirements for written description of 35 U.S.C. §112, first paragraph.

However, without wishing to acquiesce to the correctness of this rejection, and solely to expedite prosecution, the Applicants have amended claim 30 to recite a "fluorescently labeled ribonucleotide" and a "bacterial" poly(A) polymerase. The Examiner is requested to specifically address this claim in particular if this rejection is to be maintained.

In view of the foregoing discussion, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C. §103(a)

Claims 17-20, 24-26, 28-32 and 36-41 have been rejected again under 35 U.S.C. §103(a) over Martin (RNA 4:226-230, 1998) in view of Cao (PNAS 93:11580-11585, 1996) in further view of Stratagene Catalog (1988, page 39), ("Stratagene"). Specifically, the Office Action re-asserts that the yeast poly(A) polymerase methods and reagents of Martin, combined with the bacterial poly(A) polymerase of Cao and the kits of Stratagene, render the claims obvious. The Applicants respectfully traverse this rejection.

The standard for obviousness has been established over several years of court cases, such as *Graham v. John Deere*, 383 U.S. 1 148 USPQ 459 (1966), and has culminated in the guidelines set forth in §2141-§2164 of the MPEP to which the Office must adhere to when making a determination of obviousness.

According to MPEP §2142, an examiner must meet three basic criteria to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations.

As will be demonstrated below, one of skill in the art would not combine the teachings of Martin and Cao with any reasonable expectation of success. Further, Applicants respectfully submit that the Office has used impermissible standard for obviousness and has failed to successfully rebut Applicants arguments for non-obviousness.

The Office uses an impermissible standard for obviousness

In establishing this rejection and in rebutting the Applicants' arguments, the Office states that motivation to use Cao's prokaryotic poly(A) polymerase in the methods of Martin is found in Cao, who states "The identification of the gene for the second *E. coli* poly(A) polymerase opens the way for the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes". The Office Action states that one of skill in the art would have combined Cao's polymerase into Martin's methods in order to further the investigation, and, as such, one of skill in the art would have found motivation to combine the references. In other words, Cao states that the discovery of the second E. coli poly(A) polymerase gene "opens the way for a detailed investigation" of mRNA metabolism, and the Office Action submits that this investigation would lead to the claimed invention.

The Applicants respectfully submit that Cao's statement merely represents an invitation to perform a detailed exploration into mRNA metabolism using a bacterial poly(A) polymerase. This statement would not have led one of skill in the art to combine the references of Martin and Cao, and would not have led one of skill in the art towards the claimed invention. Cao's statement represents nothing more than an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation".[2]

[2] The Courts (*In re O'Farrell*, 853 F.2d 894, 903 7 USPQ2d 1673 1681 (Fed. Cir. 1988)) and the MPEP (§ 2145X.B) very clearly state that an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation" is not the standard that is used for obviousness. Such a standard "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research"." *In re Tomlinson* 363 F.2d 928, 150 USPQ 623 (CCPA 1966). As such, the test of obviousness is therefore not a determination of what prior art would have led a skilled person *to try*. In other words, any obviousness rejection that is based on an invitation to "explore a new technology...that seemed to be a promising field of experimentation" is based on an impermissible standard for obviousness.

The Office has asserted an obviousness rejection and rebutted the Applicants' arguments using Cao's statement to provide motivation to combine two references. As established above, Cao's statement merely "opens the way for a detailed investigation" and represents nothing more than an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation". Since an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation" is not the standard that is used for determining obviousness, the Office has used an impermissible standard in making this rejection, and has failed to successfully rebut the Applicant's arguments that one of skill in the art would find no motivation to combine the references of Martin and Cao.

Based on the foregoing, it is respectfully submitted that the Examiner has attempted to establish obviousness by determining what the prior art would have led a skilled person *to try*, rather than what the prior art would have let a skilled person *to do*. As such, the Office has failed to establish a proper *prima facie* case of obviousness. Further, because the Office has merely cited an "invitation to explore" to rebut the Applicant's previous arguments, the Office has failed to provide significant evidence to rebut the Applicant's arguments for non-obviousness. A mere "invitation to explore" cannot "trump" the evidence of non-obviousness previously provided by the Applicant's (see Office Action, page 9, line 6). Furthermore, as demonstrated in the Applicant's previous response, one of skill in the art would not combine the references with any reasonable expectation of success. Accordingly, this rejection of Claims 17-20, 24-26, 28-32 and 36-41 under 35 U.S.C. §103(a) may be withdrawn.

The references fail to provide a reasonable expectation of success

As previously asserted, in addition to not providing any motivation to combine the cited references, the Applicants respectfully submit that the references fail to provide any expectation of success for their combination. The Examiner assumes that one of ordinary skill in the art would have been motivated to combine the bacterial polymerase of Cao et al. with the reagents and methods of Martin et al. However, the Applicant submits that the combination of the cited references would not have provided one of ordinary skill in the art with a reasonable expectation of success. As was understood by one of ordinary skill in the art at the time the invention was made, the use of prokaryotic [*Escherichia coli*] poly(A) polymerase to attach end-label ribonucleic acids with non-radioactive labels was believed to

be impossible. For example, Rosemeyer et al. (U.S. Patent No. 5,573,913; issued November 12, 1996.) states:

> "The attachment of nucleotides to the 3' end of RNA molecules using...[*Escherichia coli*] poly(A) polymerase does...have considerable problems.... The efficient labelling of 3' ends of RNA molecules with [*Escherichia coli*] poly(A) polymerase is limited to the use of ATP and ATP derivatives since bases other than A are accepted much more poorly by the enzyme. Oligonucleotides have an extremely low efficiency as acceptor molecules. **The attachment of oligoribonucleotides to the 3' end of RNA molecules by [*Escherichia coli*] poly(A) polymerase is not known. It is not possible to attach non-radioactively labelled nucleotides**.... Therefore no process is known from the state of the art with which RNA molecules that are already present can be provided in a simple manner with one or several non-radioactive marker groups."
> [Column 1, line 58 through column 2, line 54.]

As shown by Rosemeyer et al., those of skill in the art did not believe it was possible to use a prokaryotic poly(A) polymerase to end-label a ribonucleic acid with a non-radioactively labeled ribonucleotide. Thus, any attempt to do so by combining the cited references of Martin et al. and Cao et al. would not have been made with a reasonable expectation of success.

Furthermore, as discussed in the previous response, Cao only teaches that bacterial (Escherichia coli) poly(A) polymerase has a potential use in mRNA polyadenylation. There is no mention in Cao et al. of the polyadenylation of RNA using non-radioactively labeled ribonucleotides. In contrast, the present application is directed to the end-labeling of ribonucleic acids with non-radioactively labeled ribonucleotides, of which Cao et al. is silent. Accordingly, the combined references of Martin et al. and Cao et al. fail to provide one of ordinary skill in the art with any reasonable expectation of success because the references fail to teach or suggest that a prokaryotic poly(A) polymerase could be used to end-label ribonucleic acids with non-radioactively labeled ribonucleotides.

Furthermore, as discussed in the previous response, there are many important differences between eukaryotic and prokaryotic poly(A) polymerases. For example, as is described in Sarkar, (Annu. Rev. Biochem (1997) 66:173-97), prokaryotic poly(A) polymerases do not require an upstream consensus sequence such as the AAUAAA sequence, as is required by eukaryotic poly(A) polymerases (Sarkar, pp. 182 and 193); the poly(A) tracts of prokaryotic mRNAs are significantly shorter than those of eukaryotic mRNAs

(Sarkar, pg. 175); and only a relatively small fraction of mRNA molecules are polyadenylated in prokaryotes, "in contrast to the virtually quantitative polyadenylation of most eukaryotic mRNAs." (Sarkar, pg. 175). Accordingly, the substitution of the prokaryotic poly(A) polymerase of Cao et al. into the method of Martin et al. of non-radioactive end-labeling RNA using a eukaryotic poly(A) polymerase, would not have provided one of ordinary skill in the art with any reasonable expectation of success because of the significant differences between eukaryotic and prokaryotic poly(A) polymerases and the numerous other differences between eukaryotic and prokaryotic intracellular systems as was generally known in the art at the time the invention was made.

Thus, the difficulties encountered by past researchers coupled with the significant differences between prokaryotic and eukaryotic poly(A) polymerases, would not have permitted one of ordinary skill in the art to combine the teachings of Martin et al. (fluorescent end-labeling of the 3'-end of RNA using eukaryotic poly(A) polymerase) and Cao et al. (mRNA polyadenylation using bacterial poly(A) polymerase) with any reasonable expectation of success. It was not until after the time of the Applicant's work, as reported in the present application, that one of ordinary skill in the art would have had a reasonable expectation of success in attaching non-radioactively (fluorescently) labeled ribonucleotides to the 3' end of ribonucleic acids with prokaryotic poly(A) (bacterial) polymerase.

As the Examiner has stated in this Office Action "Applicant is hereby notified that function of an enzyme and end-labeling of a substrate of that enzyme are two completely different phenomenon. In view of the Examiner's comments, how would one of skill in the art, knowing the biological function of a bacterial poly(A) polymerase be able to predict that the it would be able to end-label a substrate if the function of an enzyme and end-labeling of a substrate of that enzyme are two completely different phenomena? The Applicants respectfully submit that the Examiner's statement fully supports the Applicants' position that one of skill in the art would not be able to make such a prediction.

As previously asserted, the claimed kits are not *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because one of ordinary skill in the art would not have coupled the prokaryotic poly(A) polymerase with the non-radioactively labeled ribonucleotide in a kit for use in end-labeling ribonucleic acids, due to a lack of a reasonable expectation of success in using the two reagents together for any purpose.

Claims 27, 34, 35 and 42-44 are have been rejected under 35 U.S.C. §103(a) over Martin (RNA 4:226-230, 1998) in view of Cao (PNAS 93:11580-11585, 1996), in further view of Stratagene Catalog (1988, page 39), ("Stratagene"), and Waggoner (USPN 6,479,303). Specifically, the Office Action asserts that the yeast poly(A) polymerase methods and reagents of Martin, combined with the bacterial poly(A) polymerase of Cao, the kits of Stratagene, and the cyanine fluorophores of Waggoner, render the claims obvious. The Applicants respectfully traverse this rejection.

The Office has attempted to establish the obviousness of Claims 27, 34, 35 and 42-44 using the a similar approach as that for Claims 17-20, 24-26, 28-32 and 36-41, adding Waggoner to provide cyanine fluorophores. As established above, the Office has used an impermissible standard to establish the obviousness of Claims 17-20, 24-26, 28-32 and 36-41. Because the Office has used a similar approach to establish the obviousness of Claims 27, 34, 35 and 42-44 as Claims 17-20, 24-26, 28-32 and 36-41, the Office has also used an impermissible standard for obviousness in this rejection.

Based on the foregoing, it is respectfully submitted that the Examiner has attempted to establish obviousness by determining what the prior art would have led a skilled person *to try*, rather than what the prior art would have let a skilled person *to do*. As such, the Office has not established a proper *prima facie* case of obviousness. Furthermore, as demonstrated in the Applicant's previous response, one of skill in the art would not combine the references with any reasonable expectation of success. Accordingly, this rejection of Claims 27, 34, 35 and 42-44 under 35 U.S.C. §103(a) may be withdrawn.

CONCLUSION

The Applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 8.28.03

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